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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/018,930	12/26/2001	Masayo Kondo	029650-111	8178
21839	7590	11/01/2004	EXAMINER	
BURNS DOANE SWECKER & MATHIS L L P			KISHORE, GOLLAMUDI S	
POST OFFICE BOX 1404			ART UNIT	
ALEXANDRIA, VA 22313-1404			PAPER NUMBER	

1615

DATE MAILED: 11/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	10/018,930	KONDO ET AL.	
	<b>Examiner</b>	<b>Art Unit</b>	
	Gollamudi S Kishore, Ph.D	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 01 August 0204.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 1 and 4-18 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1 and 4-18 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |   |   |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                        | 4) <input type="checkbox"/> Interview Summary (PTO-413)                     |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)    | Paper No(s)/Mail Date. _____  |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date _____   | 6) <input type="checkbox"/> Other: _____                                    |

### DETAILED ACTION

The filing of RCE dated 8-12-04 is acknowledged.

Claims included in the prosecution are 1 and 4-18.

In view of applicant's arguments based on the calculations of molar amounts, the 102 rejections have been withdrawn.

#### *Claim Rejections - 35 USC ' 103*

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

2. Claims 1, 4-5, 7 and 10-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over EP 0 636 363.

As pointed out before EP discloses a liposomal composition, which selectively accumulates at the injured portion of vascular endothelium. The compositions contain a basic compound, a membrane forming phospholipid and a constituent of the membrane, cholesterol. Among the phospholipids taught are phosphatidylcholine, phosphatidylglycerol and acidic phosphatidic acid. The

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composition can further include surface modifying agents such as neuraminic acid (carboxyl group containing). The basic compounds include primary, secondary and tertiary amines and quaternary amines. According to EP the drug can be any drug; they include glycosaminoglycan, heparin; the diagnostic agents include X-ray contrast agents (Note the abstract, page 4, lines 19-57, page 5, lines 21-42; and Examples, Example 3 in particular). Although EP does not exemplify the invention using an acidic phospholipid or using the surface modifier, neuraminic acid, it would have been obvious to one of ordinary skill in the art to prepare liposomal compositions containing these compounds from the guidance provided by EP with the expectation of obtaining similar results. EP does not specifically teach chondroitin sulfate as the glycosaminoglycan. However, in view of EP's teachings of the use any glycosaminoglycans, one of ordinary skill in the art would have been motivated to use any glycosaminoglycan with a reasonable expectation of success.

3. Claims 1-5, 7 and 10-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over JP 09-263579 cited before.

As pointed out before, JP discloses liposomal composition containing the basic compound, piperidine derivative (claimed compound of the formula 2) to deliver a therapeutic agent to the diseased part. The liposomes contain a phospholipid, and a constituent of the membrane, cholesterol. Among the phospholipids taught are phosphatidylcholine, phosphatidylglycerol and acidic phosphatidic acid. The composition can further include surface modifying agents such as neuraminic acid (carboxyl group containing compound). Although JP does not exemplify the invention

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using the acidic phospholipid, phosphatidic acid or using the surface modifier, neuraminic acid, it would have been obvious to one of ordinary skill in the art to prepare liposomal compositions containing these compounds from the guidance provided by EP with the expectation of obtaining similar results. JP does not specifically teach chondroitin sulfate as the glycosaminoglycan. However, in view of JP's teachings of the use of any glycosaminoglycans, one of ordinary skill in the art would have been motivated to use any glycosaminoglycan with a reasonable expectation of success.

Applicant's arguments to the above 103 rejections have been fully considered, but are not found to be persuasive. First, the examiner points out that the amount of the basic compound taught in EP, according to applicant's own calculations falls within the molar percentages claimed. Applicant argues that EP merely describes the use of a hydrophilic polymer compound on the surface of a drug carrier to improve the stability in blood of the drug carrier. Applicant further argues that in EP '363 and JP '579, the compound having a positively charged portion, the hydrophilic polymer compound and the specified piperidine derivative are important film-constituent components and the other compounds used as the film-constituent component may be those commonly used in the art and attract no particular interest. Therefore, according to applicant, contrary to the Examiner's assertion, it is not within the skill of the artisan based on EP '363 and/or JP '579 to use the claimed basic compound and the claimed acidic compound in the specifically claimed amounts in order to promptly exhibit the target directive capability by a change in pH. These arguments are not found to be persuasive since EP specifically teaches that the composition taught selectively accumulates at the diseased

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site just as in instant invention and applicant; instant claims are so broad with respect to the generic term, 'basic compound' and 'acidic compound' and applicant has not shown any unexpected results using compounds falling within these broad terms. Applicant argues that the comparison between Example 9 of the present application using the specified acidic compound and Comparative Example 7 of the present application using no specified acidic compound shows that there is a significant difference in the affinity for cells of the liposome at PH 6.0. These arguments are not found to be persuasive for the following reasons. First of all, there is no statistical evaluation of the data. Secondly, a careful evaluation of data in Figures 3 and 4 which show that the composition in comparative example actually accumulates in higher amounts either at pH 6.5 or 7.4 than the composition in example 9. Instant claimed range of pH values is 5 to 7 and there are no comparative values for pH 5 and 7 (instant lower and upper limits). Finally, as pointed out above, the data in the examples are not commensurate with the scope of the claims with respect to the basic compound, acidic compound and the mole percentages.

4. Claims 8 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over EP 0 636 363 or JP 09-263579 cited above, further in view of Gold (6,465,188).

The teachings of EP and JP have been discussed above. Although these references teach the negatively charged neuraminic acid, they do not teach the inclusion of negatively charged fatty acids.

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Gold while disclosing nucleic acid ligand complexes teaches that the efficiency of delivery of the complex may be optimized by using components which enhance the fusion of the membranes and free fatty acids (carboxylate moieties) are fusion enhancing agents (note col. 14, line 66 through col. 15, line 20).

The inclusion of fatty acids in the compositions of EP or JP would have been obvious to one of ordinary skill in the art since free fatty acids enhance the delivery of nucleic acid by promoting fusion as taught by Gold.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant's arguments with regard to EP and JP have been addressed above. Applicant provides no specific arguments with regard to Gold. The rejection is maintained.

5. Claims 6 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over EP 0 636 363 in combination with either Schneider (6,258,378) and Malone (PNAS, vol. 86, pp.6077-6081, 1989).

The teachings of EP have been discussed above. Although EP teaches the use of either a primary, secondary, tertiary or quaternary amine, it does not teach claimed quaternary ammonium compounds in claim 6.

Schneider while disclosing liposomal compositions for the delivery of biologically active substances to target sites in the body of patients teaches that cationic lipids such as dimethylammoniumpropane (TAP) and dioleoyloxy propyl trimethylammonium chlorides (DOTMA) are useful in the formation of liposomes (note abstract, col. 6, lines 56-59).

Malone teaches that cationic lipids such as DOTMA enhance the liposome-mediated transfection of nucleic acids (note the abstract and the discussion).

The use of specific cationic ammonium lipids in the liposomes of EP would have been obvious to one of ordinary skill in the art since Schneider teaches their common use in the liposomes to deliver active agents to the target sites and Malone teaches that if the drug involved is a nucleic acid, the cationic lipids enhance the transfection ability of the liposomes.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant's arguments with regard to EP and JP have been addressed above. Applicant provides no specific arguments with regard to Schneider and Malone. The rejection is maintained.

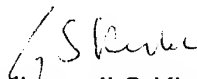
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gollamudi S Kishore, Ph.D whose telephone number is (571) 272-0598. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K Page can be reached on (571) 272-0602. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.



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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

  
Gollamudi S Kishore, Ph.D  
Primary Examiner  
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GSK